LARGE-SCALE GENOTYPING FOR THE HAPLOTYPE MAP OF THE HUMAN GENOME

RELEASE DATE: March 26, 2002

RFA: HG-02-005

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LETTER OF INTENT RECEIPT DATE: April 25, 2002

APPLICATION RECEIPT DATE: May 29, 2002

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

This is a joint initiative among several Institutes and Centers at NIH to develop a haplotype map of the human genome. This RFA solicits cooperative agreement applications for the large-scale genotyping across the genome of samples from three populations. The data will be used to develop a map of the haplotype patterns and of the genetic variants that are most informative for detecting these patterns. The haplotype map is expected to be a key resource for finding genes affecting health, disease, and response to drugs and environmental factors, and for beginning to understand the pattern of human genetic variation. It is anticipated that this initiative will become part of an international collaboration to produce a human haplotype map.

RESEARCH OBJECTIVES

Background

Biomedical researchers have developed highly successful positional cloning methods to find the genetic basis of rare diseases that are strongly affected by single genes. However, many common diseases, such as diabetes, cancer, stroke, Alzheimer's disease, Parkinson's disease, psychiatric disorders, alcoholism, heart disease, deafness, arthritis, and asthma, are influenced by multiple genetic and environmental factors. Linkage strategies that have worked well for single-gene Mendelian disorders lack power to map such polygenic susceptibility loci, and, far too often, such studies have yielded only weak linkages that fail to be confirmed in follow-up studies. Thus, relatively little is known about the genetic basis of these common diseases, or of the factors that determine individual risk of disease, clinical course, or response to treatment. Discovering the particular DNA sequence variants that contribute to common disease risk offers one of the best opportunities for illuminating pathways of disease causation in humans.

There is increasing support for the "common variant – common disease hypothesis", which proposes that most of the genetic contributions to disease susceptibility arise from variants that are relatively common in the susceptible population. A growing list of examples (ApoE4 in Alzheimer's disease, Factor V Leiden in deep vein thrombosis, MTHFR in heart disease, PPARgamma in type 2 diabetes) supports this hypothesis, which is also based on the history of our species. According to this hypothesis, a systematic case-control analysis of all common variants in the human genome would reveal the major causative genetic contributions to a disease with considerably greater statistical power than provided by the linkageapproach.

Sites in the genome where individuals differ in their DNA sequence by a single base are called single nucleotide polymorphisms (SNPs). Recent work has shown that there are about 10 million SNPs that are common in human populations. SNPs are not inherited independently; rather, sets of adjacent SNPs are inherited in blocks. The specific pattern of particular SNP alleles in a block is called a haplotype. Recent studies show that most haplotype blocks in the human genome have been transmitted through many generations without recombination. Furthermore, each block has only a few common haplotypes. This means that although a block may contain many SNPs, it takes only a few SNPs to uniquely identify or "tag" each of the haplotypes in the block.

Recent studies show that most common haplotypes occur in all human populations, though the frequencies may vary. Initial studies also indicate that the boundaries between the blocks are remarkably similar among the populations studied, although some of the blocks found in

European or Asian populations are subdivided into separate blocks in populations of African ancestry, as would be expected based on the more recent history of European and Asian populations compared with African ones. These data provide strong support for the idea that a human haplotype map built with samples from populations of African, Asian, and European ancestry would apply to most populations in the world, although further testing of this conclusion is needed. Although the block boundaries seem to be similar in the various populations, the frequencies of the haplotypes and the associations between blocks do differ among populations, so the optimum choice of tag SNPs will need to be based on information from a number of populations.

The present initiative will support the development of the haplotype map, abbreviated the HapMap, which will be a description of the set of haplotype blocks and the SNPs that tag them. The HapMap is expected to be valuable by reducing the number of SNPs required to examine the entire genome for association with a phenotype from 10 million SNPs to roughly 300,000 tag SNPs. This should make genome scan approaches to finding regions with genes that affect diseases much more efficient and comprehensive, since effort will not be wasted typing more SNPs than necessary and all regions of the genome can be included.

In addition to its use in studying genetic associations with disease, the HapMap is expected to be a powerful resource for studying the genetic factors contributing to variation in response to environmental factors, in susceptibility to infection, in host immune responses, and in the effectiveness of and adverse responses to drugs and vaccines. All such studies will be based on the expectation that there will be higher frequencies of the contributing genetic components in a group of people with a disease or particular response to a drug, vaccine, pathogen, or environmental factor than in a group of similar people without the disease or response. Using just the tag SNPs, researchers should be able to find chromosome regions that have different haplotype distributions in the two groups of people, those with a disease or response, and those without. Each region would then be studied in more detail to discover which variants in which genes in the region contribute to the disease or response. This, in turn, is expected to contribute to an understanding of the complex biological processes involved in the disease or response, leading to more effective interventions or control measures. This should also allow the development of tests to predict which drugs or vaccines would be most effective in individuals with particular genotypes for genes affecting drug metabolism.

Haplotype methods have already been used successfully for finding genes contributing to disease. Examples include some rare single-gene disorders such as cystic fibrosis, diastrophic

dysplasia, and Hirschsprung's disease, as well as more common diseases such as Crohn's disease, type 2 diabetes, psoriasis, and migraine.

An initial meeting to discuss the HapMap Project was held in July 2001; the report of this meeting is available at http://www.nhgri.nih.gov/About_NHGRI/Der/haplotype/index.html. Since then, working groups have been discussing the experimental design, the populations to include, and the ethical, legal, and social issues (ELSI) that must be addressed when collecting samples from identified populations.

Pilot studies have already shown sufficient differences in haplotype frequencies among Yoruban, CEPH (Western and Northern European ancestry), and Japanese/Chinese samples to warrant beginning to develop the HapMap with large-scale analysis of haplotypes in these populations. NHGRI is arranging for additional sample collection for these populations. These populations were chosen based on a sampling of ancestral geography, and they are not to be considered typical, special, or well defined. In addition, a few non-human primate samples may be included because they define the ancestral allele and thus help in the interpretation of human SNP patterns. It is anticipated that the international HapMap Project will study roughly 200 samples from these three populations across the genome. NIH-funded researchers are expected to contribute 30-50% of this effort. Support from other public and private sources is expected to be forthcoming.

Research Scope

The goal of the HapMap Project is to develop a genome-wide haplotype map by identifying the haplotype blocks and the common haplotypes in the human genome, and to define a set of tag SNPs, using the population samples discussed above. This RFA is intended to solicit research proposals for the large-scale genotyping and analysis of SNPs needed to create the first-generation HapMap. About 600,000 informative SNPs will need to be genotyped across the genome in all the samples in order to find the roughly 300,000 tag SNPs of the HapMap.

Each research group will be responsible for the genotyping of particular regions of the genome, in all of the samples. Each research group will choose which known SNPs in those regions will be genotyped, will obtain more SNPs in those regions if needed, and will genotype the SNPs. Each research group will participate in the analysis group that will develop methods to analyze the genotype data to find haplotypes and haplotype blocks and to choose tag SNPs. The data will be deposited quickly in public databases.

Projects supported by this RFA will be part of a HapMap Network set up with the funded groups. Coordination of the overall project will be through a Coordinating Committee composed of the investigators and representatives of the funding agencies. This network may also coordinate with related projects fundedby other organizations.

The Coordinating Committee will be responsible for a number of components of the HapMap Project, including advising the NHGRI about which populations to study and the number of samples from each population to be studied, in consultation with the ELSI/Population working group; and recommending which chromosome regions each awardee will be responsible for, taking into account the awardees' preferences and capacities. To address particular issues, the Coordinating Committee may establish groups as needed, which will include representatives from the grantees, the funding agencies, and possibly other experts. Such groups might include an analysis group to develop methods to analyze the data; a quality group to develop methods to assess data quality; and a communication group for explaining the project. The awardees will be expected to cooperate closely with each other and the funding agencies.

Other Components of the HapMap Project (not part of this RFA)

This RFA deals only with the large-scale genotyping and analysis for the HapMap. However, the overall project will have several other components: 1) Study of the haplotype patterns on a small scale (in a few dozen regions) in several populations in addition to those to be included in the initial large-scale analysis. NHGRI is arranging for the community engagement and sample collection for about 10 populations; more populations may be included in the future. Based on the results of these small-scale studies, some of these populations may also be studied on a large scale in the future. 2) Obtaining more SNPs, which will be used for developing the HapMap and will be studied when particular regions are identified by the use of the HapMap as potentially affecting a disease or response. 3) Developing better and cheaper genotyping methods, to allow average-sized laboratories to use the HapMap to study many diseases and responses. 4) Developing better statistical methods to analyze data on SNPs, haplotypes, environments, and disease associations. 5) Addressing the ethical,legal, and social issues raised by the HapMap.

MECHANISM OF SUPPORT

This RFA will use the NIH U54 Specialized Center Cooperative Agreement and the U01 Research Project Cooperative Agreement award mechanisms, in which the Principal Investigators retain the primary responsibility and dominant role for planning, directing, and executing the HapMap Project, with NIH staff being substantially involved as a partner with the

Principal Investigators, as described under the section "Cooperative Agreement Terms and Conditions of Award". This RFA is a one-time solicitation, and uses just-in-time concepts. The earliest anticipated award date is September 20, 2002.

FUNDS AVAILABLE

The NIH intends to commit approximately $16 million total costs in FY 2002 to fund two to four awards in response to this RFA; a similar amount is expected to be committed for the second year of the awards. An applicant may request a project period of up to two years. Although the financial plans of the ICs provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. Each research group will be subject to a semi-annual evaluation of progress by the Scientific Advisory Panel of the HapMap Network (see below for details). Based on this evaluation, adjustments may be made in funding levels if any groups fail to meet their goals.

ELIGIBLE INSTITUTIONS

Domestic organizations may submit applications if they have any of the following characteristics:

o For-profit or non-profit organizations.
o Public or private institutions, such as universities, colleges, hospitals, and laboratories.
o Units of State and local governments.
o Eligible agencies of the Federal government.
(Foreign organizations are not eligible to submit applications, but are eligible to receive subcontracts in applications submitted by domestic organizations.)

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institutions to develop applications for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

In order to complete the large-scale aspect of the HapMap within two years and at reasonable cost, only investigators who have demonstrated experience with large-scale SNP genotyping will be eligible to apply. Applicants should have genotyped at the rate of 100,000 high-quality

genotypes per month for at least three months. Each applicant should have the capability to do at least 10% of the genotyping for this project in two years.

SPECIAL REQUIREMENTS

NHGRI POLICIES CONCERNING INTELLECTUAL PROPERTY, DATA RELEASE, AND DATA QUALITY

Over the past several years, NHGRI has established a number of policies related to large-scale data production (http://www.nhgri.nih.gov/Grant_info/Funding/Statements/RFA/intellectual_property.html, http://www.nhgri.nih.gov:80/Grant_info/Funding/Statements/RFA/data_release.html, http://www.nhgri.nih.gov/Grant_info/Funding/Statements/data_release.html). Similar policies related to this initiative are under development. NHGRI is currently consulting with a number of advisors, including haplotype producers and users aswell as the National Advisory Council for Human Genome Research, to develop policies that will ensure the timely public release of genotype and haplotype-related data produced under this initiative. The intent is for research supported under this RFA to produce a haplotype map that will be freely available to all investigators. Applicants will need to describe their plans for releasing data to public databases, including dbSNP. However, precise terms and conditions will be negotiated when the awards are made.

An important component of the NHGRI's large-scale production programs has been the establishment of quality standards and the assessment of the quality of the data produced. NHGRI intends to establish a process to assess the quality of the genotyping data produced by the HapMap Network, based on quality measure developed by the Coordinating Committee. Since the quality of the genotyping data that a research group has produced over the last year is likely to be a reasonable general indicator of the quality of the genotyping data that it will produce, applicants should describe the quality of their genotyping data and how it was assessed.

SPECIAL REQUIREMENTS FOR COOPERATIVE AGREEMENTS

Cooperative Agreement Terms and Conditions of Award

The following terms and conditions will be incorporated into the award statement of each cooperative agreement awarded under RFA HG-02-005 and will be provided to the Principal Investigators and the appropriate institutional officials at the time of award. The following special

terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, DHHS grant administration regulations at 45 CFR Parts 74 and 92, as are other DHHS, NIH, and NIH grant administration policies:

1. Cooperative Agreement

The administrative and funding instruments used for this program will be the Specialized Center Cooperative Agreement (U54) and the Research Project Cooperative Agreement (U01). The cooperative agreement is an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH scientific and programmatic involvement with the awardee is anticipated during the performance of the activity. Under the Cooperative Agreement, the NIH purpose is to support and stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the project as a whole will reside with the awardees, although specific tasks and activities in carrying out the study will be shared among the awardees and the NIH Program Director.

2. P.I. Rights and Responsibilities

The P.I. will have the primary responsibility for defining the details for the project within the guidelines of RFA HG-02-005 and for performing the scientific activities. The P.I. will agree to accept close coordination, cooperation, and participation of NIH staff in those aspects of scientific and technical management of the project as described under "NIH Program Staff Responsibilities".

The P.I. of a HapMap genotyping research group will:
o Determine experimental approaches, design protocols, set project milestones, and conduct experiments.
o Ensure that the amount of genotyping agreed upon is accomplished.
o Ensure that the genotyping meets or betters the cost agreed upon.
o Submit data for quality assessment in any manner specified by the Coordinating Committee or the Scientific Advisory Panel.
o Ensure that the genotyping quality meets or exceeds the standards agreed to by the Coordinating Committee and the Scientific Advisory Panel.
o Ensure that the choice of SNPs to genotype is done by the methods agreed to by the Coordinating Committee and the Scientific Advisory Panel.

o Ensure that the analyses of haplotypes, haplotype blocks, and tag SNPs is done by the methods agreed to by the Coordinating Committee or the Scientific Advisory Panel.
o Ensure that the data resources developed as part of this project, including individual genotypes, haplotypes, haplotype blocks, and tag SNPs, are released according to NHGRI policies, by procedures developed by the Coordinating Committee, and that results are submitted to dbSNP.
o Adhere to the NHGRI policies regarding intellectual property and other policies that might be established during the course of this activity.
o Submit periodic progress reports in a standard format, as agreed upon by the Coordinating Committee and the Scientific Advisory Panel.
o Accept and implement the common guidelines and procedures approved by the Coordinating Committee.
o Accept and participate in the cooperative nature of the group.
o Attend Coordinating Committee meetings.
o Coordinate and collaborate with other U.S. and international groups producing the HapMap.

3. NIH Program Staff Responsibilities

The NIH Program Director is a scientist of the NHGRI extramural staff who will provide normal stewardship of the award and, in addition, will have substantial scientific and programmatic involvement during the conduct of this activity through technical assistance, advice, and coordination. However, the role of NIH staff will be to facilitate and not to direct the activities. It is anticipated that decisions in all activities will be reached by consensus of the HapMap Network and that NIH staff will be given the opportunity to offer input to this process. One NIH Program Director will participate as a member of the Coordinating Committee and will have one vote. The Program Director will have the following substantial involvement:
o Participate with the other Coordinating Committee members in the group process of setting research priorities, deciding optimal research approaches and protocol designs, and contributing to the adjustment of research protocols or approaches as warranted. The Program Director will assist and facilitate the group process and not direct it.
o Serve as a liaison, helping to coordinate activities among and for the awardees, including acting as a liaison to the NHGRI and the other Institutes and Centers of the NIH, and as an information resource about extramural genome research activities. The Program Director will also coordinate the efforts of the HapMap Network with other U.S. and international groups participating in the HapMap Project.
o Attend all Coordinating Committee meetings as a voting member and assist in developing operating guidelines, quality control procedures, and consistent policies for dealing with recurrent situations that require coordinated action.

The Program Director must be informed of all major interactions of members of the Coordinating Committee. The NIH Program Director will be responsible for scheduling the time and preparing concise minutes or summaries of the Coordinating Committee meetings, which will be delivered to members of the group within 30 days after each meeting.

o Report periodically on the progress of the HapMap Project to the Directors of the NHGRI and other NIH Institutes and Centers.

o Provide relevant expertise and overall knowledge of NIH-sponsored research to facilitate the selection of scientists not affiliated with the awardee institutions who are to serve on the Advisory Panel and the Coordinating Committee.

o Serve as a liaison between the Coordinating Committee and the Advisory Panel, attending Advisory Panel meetings in a non-voting liaison member role.

o Serve on subcommittees of the Coordinating Committee and the Advisory Panel, as appropriate.

o Assist awardees in the development, if needed, of policies for dealing with situations that require coordinated action.

o Provide advice in the management and technical performance of the investigation.

o Assist in promoting the availability of the HapMap and related resources developed in the course of this project to the scientific community at large.

o Retain the option to recommend, with the advice of the Scientific Advisory Panel, the withholding or reduction of support from any project within the HapMap Network that substantially fails to achieve its genotyping goals at the cost agreed to or the quality agreed upon by the Coordinating Committee, fails to remain state of the art in its genotyping capabilities, or fails to comply with the Terms and Conditions of the award.

o Participate in data analyses, interpretations, and, where warranted, co-authorship of the publication of results of studies conducted through the HapMap Network.

4. Collaborative Responsibilities

The Coordinating Committee will serve as the main governing board of the HapMap Network established under this RFA. It is anticipated that additional coordination mechanisms will be set up with other U.S. and international groups that may join this effort. The Coordinating Committee membership will include one NIH Program Director and the P.I. from each awarded cooperative agreement. The Coordinating Committee may add additional members. Other government staff may attend the Coordinating Committee meetings, if their expertise is required for specific discussions.

The Coordinating Committee will be responsible for coordinating with other groups working on the HapMap and for advising NIH as to how the HapMap Network can help complete the first phase of the HapMap within the stated goals of time and accuracy, and within budget. To address particular issues, the Coordinating Committee may establish groups as needed, which will include representatives from the grantees and the funding agencies, and possibly other experts. Such groups might include an analysis group to develop uniform methods to choose SNPsfor study, define haplotype blocks and haplotypes, and choose the tag SNPs, as well as develop overall analyses of the data; a quality group to develop quality standards and methods to assess data quality; and a communication group to develop principles for explaining the project and reporting findings. The Coordinating Committee will develop procedures for data flow to ensure quality checks of the data and deposition in public databases. Members of the Coordinating Committee will be required to accept and implement the common guidelines and procedures approved by the Coordinating Committee.

5. Scientific Advisory Panel

A Scientific Advisory Panel may be established to evaluate the progress of the HapMap Network toward producing the first phase of the HapMap by October 2004. The Scientific Advisory Panel will provide recommendations to the Directors of NHGRI and the other participating Institutes and Centers about continued support of all components of the program. The Scientific Advisory Panel will be composed of three to five senior scientists with relevant expertise, although the membership may be enlarged permanently or on an ad hoc basis as needed.

The Scientific Advisory Panel will meet at least twice a year; some meetings may be by telephone conference. The first part of the meeting will be a joint meeting with the Coordinating Committee to allow the members of the two committees to interact directly with each other. Twice a year the Scientific Advisory Panel will make recommendations regarding progress of the HapMap Network and present advice to the Directors of NHGRI and the other participating Institutes and Centers about changes, if any, that may be necessary in the HapMap Network program. If other funding agencies fund projects with the same goal as this RFA, the Advisory Panel may be modified to accommodate this situation by mutual consent of the agencies involved.

6. Arbitration Process

Any disagreement that may arise on scientific or programmatic matters within the scope of the awards between award recipients and the NIH may be brought to arbitration. An Arbitration Panel will be convened, which will be composed of three members: (1) a designee of the

awardee, (2) an NIH designee, and (3) a third designee with relevant expertise who is chosen by the other two. The Arbitration Panel will help resolve scientific or programmatic issues that develop during the course of work that restrict progress. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with NIH regulations 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16.

7. Semi-Annual Milestones

All awardees participating in the HapMap Network will be asked to define semi-annual milestones at the time of the award and to update these milestones every six months. These will be made a condition of the award. In accord with the procedures described above, NIH may withhold or reduce funds for projects that substantially fail to meet their milestones or to maintain the state of the art.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific or research, peer review, and financial or grants management issues:

o Direct your questions about scientific and research issues to:

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Karen Hofman, M.D.
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o Direct your questions about peer review issues to:

Rudy Pozzatti, Ph.D.
Scientific Review Branch
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Telephone: (301) 402-8739
Fax: (301) 435-1580
rudy_pozzatti@nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Jean Cahill
Grants Administration Branch
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Telephone: (301) 402-0733
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LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research
o Name, address, e-mail, and telephone number of the Principal Investigator
o Names of other key personnel

o Participating institutions
o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information it contains allows NIH staff to estimate the potential review workload and plan the review.

The letter of intent should be e-mailed by April 25, 2002, to:

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SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo at (301) 435-0714 or GrantsInfo@nih.gov.

SUPPLEMENTAL INSTRUCTIONS

SPECIAL APPLICATION GUIDANCE FOR PRODUCTION GENOTYPING

Applicants should address the following when preparing applications for the genotyping production projects called for in this RFA. Items A–D in the application should not exceed 25 pages.

I. Prior Experience (as part of item C in the application)

In order to complete the large-scale aspect of the HapMap within two years and at reasonable cost, only investigators who have demonstrated experience with large-scale SNP genotyping will be eligible to apply. Applicants should have genotyped at the rate of 100,000 high-quality genotypes per month for at least three months.

The NHGRI has conducted several competitions for large-scale projects during the past few years. Our experience has been that specific information items are central to the review of large-scale production proposals, and that the most highly rated applications provided that information clearly and succinctly. Brief, concise answers are encouraged. Please focus these answers on your past accomplishments.

How do your group's past efforts support its ability to successfully contribute to the HapMap? Discussion should include, but not be limited to:

Prior experience in SNP genotyping: How much genotyping per month has your group done in the last three (or more) months? How much genotyping did your group do in the last year? What proportion of the genotyping reactions worked successfully?

Prior experience with genotype quality: Describe the quality of the genotypes your group produced, how your group checked this quality, and how the quality information was used to improve the genotyping quality.

Prior experience with increasing throughput and reducing costs: Describe how your group managed to increase capacity and decrease costs for large-scale genotyping, sequencing, or other large-scale genomic projects.

Prior experience in attaining milestones: What examples can you provide that you have proposed milestones for genotyping, sequencing, or other large-scale genomic projects and met them on schedule? What internal metrics have you used to evaluate progress?

II. Research Proposal (as part of item D in the application)

Genotyping capacity: Although the actual numbers may vary, assume for this application that the total amount of genotyping in the first phase of the HapMap will be 600,000 informative SNPs in each of about 200 individuals. Each applicant should have the capability to do at least 10% of the genotyping for this project in two years. Applicants should propose the amount of genotyping they wish to carry out; the actual amounts will be negotiated when the awards are made.

Applicants may propose the chromosome regions they wish to genotype and analyze. Allocations of the regions will be negotiated among the groups and the Coordinating Committee after the awards are made.

Genotyping platform: Applicants should propose and justify the genotyping platform they wish to use. It is desirable to have a variety of platforms used for this project, and a common platform is not expected to be chosen.

Genotype production plan: The applicant should present a plan to implement large-scale genotyping, and propose milestones for achieving the proposed genotyping production. This plan should thoroughly discuss and justify the applicant's specific choices for all phases of the genotyping pipeline, including choosing SNPs to study, obtaining needed SNPs in regions, developing genotyping assays, producing primers, genotyping, assessing quality, finding blocks and haplotypes, choosing tag SNPs, and depositing genotype and haplotype data in dbSNP. It will be important to discuss potential bottlenecks or other problems that may be anticipated and how they will be addressed. Applicants should make clear how much of a ramp-up the proposed production plans are from their current production capacity.

Genotyping costs: Include all costs for genotyping production. The calculated costs of genotyping should take into account all the expenses associated with large-scale high-quality genotyping, including choosing SNPs, obtaining needed SNPs, developing genotyping assays, producing primers, genotyping, repeating failed genotyping reactions, assessing quality, analyzing the data, and depositing the data. The total costs should also include any production-related technology development that will be supported by the project. Applicants should also provide a breakdown of costs so that the reviewers can evaluate the contribution of different cost elements, such as personnel, equipment, reagents and consumables, and production-related technology development, to the reported total cost. Applicants should explain how they anticipate reducing costs in the first and second years of the awards. Cost analyses should be presented in terms of both direct costs and total costs, which include indirect costs. Applicants should explain how they monitor costs internally.

Analysis costs: Costs for the analysis of the genotypes to find haplotypes, haplotype blocks, and tag SNPs should be included.

Other costs: Costs for the PI and another individual to attend two meetings a year of the HapMap Network should be included.

Obtaining SNPs: Most of the common SNPs needed for developing the HapMap should be available by the time the awards under this RFA start. More SNPs may still be needed in particular regions, however, and applicants should describe how they would obtain additional SNPs.

Genotype quality: Applicants should describe how they would monitor the quality of the genotypes they propose to produce. Internal quality control programs should be described, including quality assessment criteria. Applicants should be prepared to submit genotyping data produced in the last six months, including success rates, quality measures, and information about data tracking, prior to review if NHGRI and the reviewers decide that data quality needs to be assessed in more detail. This decision will be made after the reviewers have seen the applications.

Data analysis: It is anticipated that an analysis group will be formed and that there will be a coordinated approach to data analysis and definition of blocks, haplotypes, and tag SNPs. Applicants should describe the expertise and experience their groups have with these sorts of analyses and how they would approach them.

Data release: Applicants should describe their proposed data release policy.

Management plan: Applicants should describe how this project would be managed.
Since the management of this project would require a significant time commitment, a P.I. is expected to devote at least 30% effort to this project.

III. Human Subjects (as part of item E in the application)

Applicants should address human subjects issues. The samples to be used for this project will have been collected after a process of community engagement and individual informed consent for participation in the HapMap Project. The samples to be used will be publicly available through the NIGMS Human Genetic Cell Repository at the Coriell Institute. Thus, while the research funded under this RFA will involve Human Subjects, NHGRI expects that most IRBs will find that exemption 4 applies (the study of existing samples in which the human subjects are not identifiable, directly or through identifiers linked to the subjects).

Applicants should address inclusion issues. Of the samples to be studied, at least one-quarter will come from African populations and at least one-quarter will come from Asian populations, so

there will be a large minority representation. Roughly equal numbers of females and males will be studied. Children from ages 18 to 21 will be included.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed original of the application, including the Checklist, and three signed photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, send two additional copies of the application to:

Rudy Pozzatti, Ph.D.
Scientific Review Branch
National Human Genome Research Institute
Building 31, Room B2B37
Bethesda, MD 20892-2032
Telephone: (301) 402-8739
Fax: (301) 435-1580
rudy_pozzatti@nih.gov

APPLICATION PROCESSING: Applications must be received by May 29, 2002. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as

one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NHGRI. Incomplete or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NHGRI. As part of the initial merit review, all applications:
o Will receive a written critique;
o May undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score;
o Will receive a second level review by the National Advisory Council for Human Genome Research.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and

thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

The application must be directed toward attaining the programmatic goals as stated under RESEARCH OBJECTIVES. The following criteria will be used by peer review groups to evaluate these applications:

(1) SIGNIFICANCE: Does the application address the problem outlined in this RFA?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project as outlined in this RFA? Are potential problem areas acknowledged and alternative tactics considered? Are the plans for scaling up production adequate? Are the costs appropriate and are the plans for reducing costs adequate? Are the plans for assessing data quality adequate? Is the proposed effort likely to produce an adequate amount of high-quality genotype and haplotype information?

(3) INNOVATION: Does the project employ novel concepts, approaches, or methods for genotyping, haplotyping, or analysis of SNP, genotype, or haplotype data, if appropriate? Does the project develop new methods or technologies to reduce costs or increase quality or throughput?

(4) INVESTIGATOR: Are the principal investigator, key personnel, and any collaborators appropriately trained and well suited to carry out this work? Is the work proposed appropriate for the experience of the P.I., key personnel, and any collaborators? Does the prior experience section provide sufficient evidence that the research group can carry out its part of the project? Are the management plan and P.I. experience with management sufficient for this project?

(5) ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment? Are any collaborative arrangements appropriate? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

o PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

o INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research.

o DATA SHARING: The adequacy of the proposed plan to share data in a timely manner.

o BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: April 25, 2002
Application Receipt Date: May 29, 2002
Peer Review Date: July 2002
Council Review: September 2002
Earliest Anticipated Start Date: September 25, 2002

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit, as determined by peer review.
o Plans for data release and intellectual property.
o Variety in genotyping platforms, if appropriate.
o Cost-effectiveness.
o Availability of funds.
o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some

circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at: http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.172, 93.394, 93.867, 93.866, 93.855, 93.856, 93.891, 93.846, 93.287, 93.173, 93.121, 93.848, 93.847, 93.849, 93.279, 93.114, 93.862, 93.242, 93.853, 93.989 and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development

services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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